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Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome: An Evidence-Based Review

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A B S T R A C T

Purpose

Tumor lysis syndrome (TLS) has recently been subclassified into either laboratory TLS or clinical TLS, and a grading system has been established. Standardized guidelines, however, are needed to aid in the stratification of patients according to risk and to establish prophylaxis and treatment recommendations for patients at risk or with established TLS.

Methods

A panel of experts in pediatric and adult hematologic malignancies and TLS was assembled to develop recommendations and guidelines for TLS based on clinical evidence and standards of care. A review of relevant literature was also used.

Results

New guidelines are presented regarding the prevention and management of patients at risk of developing TLS. The best management of TLS is prevention. Prevention strategies include hydration and prophylactic rasburicase in high-risk patients, hydration plus allopurinol or rasburicase for intermediate-risk patients, and close monitoring for low-risk patients. Primary management of established TLS involves similar recommendations, with the addition of aggressive hydration and diuresis, plus allopurinol or rasburicase for hyperuricemia. Alkalinization is not recommended. Although guidelines for rasburicase use in adults are provided, this agent is currently only approved for use in pediatric patients in the United States.

Conclusion

The potential severity of complications resulting from TLS requires measures for prevention in high-risk patients and prompts treatment in the event that symptoms arise. Recognition of risk factors, monitoring of at-risk patients, and appropriate interventions are the key to preventing or managing TLS. These guidelines should assist in the prevention of TLS and improve the management of patients with established TLS.

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INTRODUCTION

Tumor lysis syndrome (TLS) is characterized by a group of metabolic derangements caused by the massive and abrupt release of cellular components into the blood after the rapid lysis of malignant cells.[1] It is observed most frequently in patients with hematologic malignancies such as acute lymphoblastic leukemia (ALL) and Burkitt's lymphoma after the initiation of cytotoxic therapy, although it may also occur spontaneously and/or in other tumor types with a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy. The release of intracellular metabolites, including nucleic acids, proteins, phosphorus, and potassium, can overwhelm normal homeostatic mechanisms, potentially leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia.

The crystallization of uric acid or calcium phosphate in renal tubules can further result in impaired renal function. In some cases, TLS can lead to acute renal failure and even death.

The keys to the prevention and management of TLS include awareness of its causes, physiologic consequences, and predisposing risk factors and identification of high-risk patients. Implementation of appropriate prophylactic measures, vigilant monitoring of electrolyte levels in patients undergoing chemotherapy, and initiation of more active treatment measures when necessary are also essential.[1] Because of the serious and potentially fatal consequences of TLS, an international panel of experts was assembled to develop a set of guidelines for the stratification of patients according to risk, optimal use of prophylactic measures, and implementation of appropriate treatments.

METHODS

Panel Composition

The panel was composed of experts in clinical oncology, with a focus on expertise in pediatric and/or adult hematologic malignancies and the management of TLS (Appendix, online only). In addition, a representative from the Multinational Association of Supportive Care in Cancer was included as a consultant.

Process Overview

A subset of the panel initially met to outline specific areas to be addressed by the guidelines and to develop detailed recommendations based on currently available clinical evidence as well as standards of practice. Group discussion and consensus was required for each recommendation. Systematic assessment of the level of evidence and grading of recommendations was included in the process. Once a draft of the guidelines had been approved, the guidelines were circulated to the full panel for their input and endorsement. All members of the panel were given the opportunity to comment on the proposed guidelines and the data supporting each recommendation.

Literature Review and Data Collection

Relevant publications based on searches of MEDLINE (National Library of Medicine, Bethesda, MD) through January 2006 and reference lists of published articles were examined for the creation of these guidelines. In addition, meeting abstracts available through this date were included in the literature review.

BACKGROUND

Pathogenesis and Clinical Consequences

In malignancies with a high proliferative rate, large tumor burden, and high sensitivity to chemotherapy, the initiation of cytotoxic chemotherapy, cytolytic antibody therapy, and/or radiation therapy can cause the rapid lysis of tumor cells, leading to the release of massive quantities of intracellular contents into the bloodstream, including anions, cations, proteins, and nucleic acids.[2] The release and subsequent catabolism of nucleic acids can result in hyperuricemia.[1-4] Specifically, purine nucleic acids are catabolized to hypoxanthine, then xanthine, and finally to uric acid by the enzyme xanthine oxidase (Fig 1). Under normal conditions, uric acid is cleared through the kidneys at a rate of approximately 500 mg/d.[5] Uric acid has a pKa of 5.4 to 5.7, and it is poorly soluble in H_2O. In the distal tubules and collecting system of the kidney, the pH of urine is approximately 5, and the solubility of uric acid at this pH is approximately 15 mg/dL.[6] Thus in hyperuricemic conditions, as the concentration of uric acid increases, the likelihood of crystal formation and deposition increases. The precipitation of uric acid in the renal tubules may then lead to renal insufficiency or failure.[7-9]

In a retrospective review of 83 patients with non-Hodgkin's lymphoma (NHL) admitted for treatment from 1995 to 2000 at the Henry Ford Hospital, Cairo et al[10] reported an association between uric acid levels and the risk of developing TLS or renal events. TLS was defined as the presence of two or more abnormal laboratory values simultaneously, for uric acid, creatinine, phosphate, potassium, and calcium. The relative risk of developing TLS was significantly higher in patients with high uric acid levels ($\geq$ 8 mg/dL) as compared with those with medium uric acid levels ($\geq$ 4 but $<$ 8 mg/dL; relative risk [RR] = 4.03; $P < .0001$), which in turn was higher than for patients with low uric acid levels ($<$ 4 mg/dL; RR = 11.66; $P < .0001$). In addition, the risk of renal events was significantly increased in patients with high versus
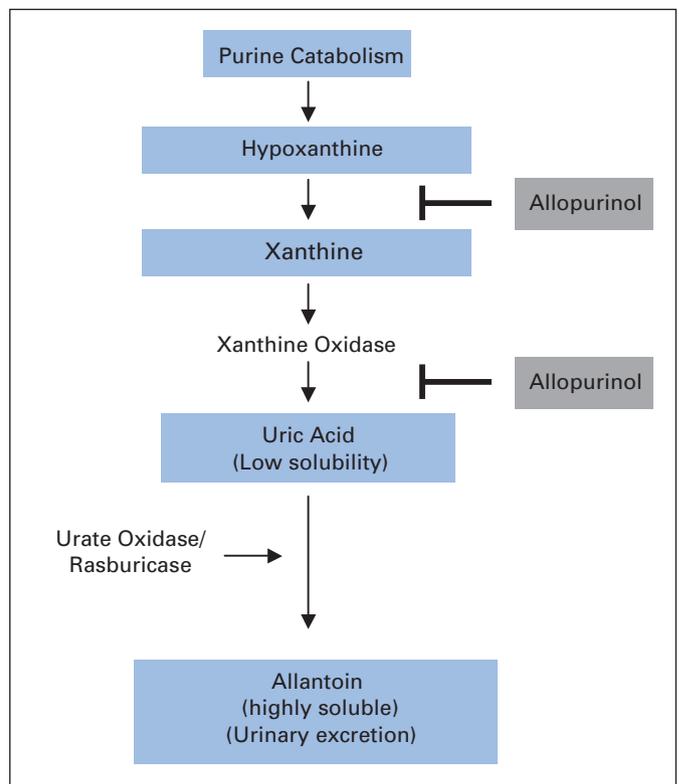

Fig 1. Purine catabolism pathway. Purines are catabolized to hypoxanthine and xanthine by the enzyme xanthine oxidase, which can be inhibited by allopurinol. These intermediaries are further converted to uric acid, which is the final step in purine catabolism in humans. However, in most other mammals, there exists an enzyme, urate oxidase, which further converts uric acid to the more soluble allantoin. Rasburicase is a recombinant form of urate oxidase.

low or medium uric acid levels (RR = 10.7; $P < .00009$). Finally, when logistic regression analysis was performed, they found that the risk of TLS increased by 1.75-fold for every milligram per deciliter increase in uric acid ($P < .0001$), and the risk for renal events increased by 2.21-fold ($P = .0012$).

The levels of phosphorus in malignant cells can be up to four times the levels found in normal cells, and rapid release of these stores can result in hyperphosphatemia ($\geq$ 2.1 mmol/L [children] or $\geq$ 1.45 mmol/L [adults]).[7] Initially, the kidneys respond by increasing urinary excretion and decreasing tubular resorption. However, tubular transport mechanisms eventually become overloaded, leading to increasing serum phosphorus levels. Acute renal insufficiency caused by uric acid or other complications may further exacerbate the development of hyperphosphatemia.[11] In severe cases, hyperphosphatemia can lead to nausea, vomiting, diarrhea, lethargy, or seizures. In addition, because the risk of calcium phosphate precipitation increases when the calcium-phosphorus multiple exceeds 70,[7,12,13] hyperphosphatemia can increase the precipitation of calcium-phosphate in renal tubules, a process which can lead to, or exacerbate, renal failure, creating a vicious cycle.[14] Further, the precipitation of calcium can lead to secondary hypocalcemia, which may be either symptomatic or asymptomatic.[7,12-14] In extreme cases, hypocalcemia can result in cardiac arrhythmia, hypotension, tetany, and muscular cramps.[15]

The rapid release of potassium can lead to hyperkalemia, which may be exacerbated by renal failure, or may be secondary to the excess

administration of potassium during induction therapy.[16] Elevated potassium levels can produce cardiac irregularities such as arrhythmias, ventricular tachycardia, fibrillation, or cardiac arrest.[15] In addition, high levels of potassium may also produce neuromuscular effects, including muscle cramps and paresthesia.

Uremia (characterized by abnormally increased blood urea nitrogen) is commonly associated with TLS and may be caused by multiple mechanisms, most commonly the deposition of uric acid crystals in renal tubules.[7-9] However, uremia may also be caused by calcium phosphate precipitation, xanthine crystallization, tumor infiltration in the kidney, tumor-associated obstructive uropathy, drug-associated nephrotoxicity, and/or acute sepsis.

Clinical manifestations of TLS may include nausea, vomiting, diarrhea, anorexia, lethargy, edema, fluid overload, hematuria, congestive heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and possible sudden death.[1,15] Although symptoms may occur before the start of chemotherapy, they are observed more commonly within 12 to 72 hours after the initiation of cytoreductive therapy. Complications resulting from TLS can compromise the efficacy or further administration of chemotherapy.[3]

Classification

Although the set of metabolic abnormalities comprising TLS is generally agreed on, there is currently no universally accepted system for classification and grading. The National Cancer Institute Common Toxicity Criteria 2.0 system and the Common Terminology Criteria for Adverse Events 3.0 grade TLS by its presence (grade 3) or death (grade 4; Common Terminology Criteria for Adverse Events only). Hande and Garrow[4] developed a classification system based on defining laboratory or clinical TLS (LTLS or CTLS). This system distinguishes between patients who do not require therapeutic intervention versus those experiencing life-threatening clinical abnormalities. However, there are several shortcomings inherent in this system. First, an increase in laboratory values of 25% above baseline is required, which does not take into account patients with preexisting abnormal values. Second, the Hande-Garrow system requires that changes occur within 4 days of the initiation of therapy, which again does not account for patients who present with TLS or who develop it before therapy initiation or after 4 days.

To address these shortcomings, Cairo and Bishop[5] developed a system for defining CTLS and LTLS based on modifications to the Hande-Garrow classification. This classification and grading system is currently being included in the ongoing Children's Oncology Group study ANHL01P1 in children with newly diagnosed advanced-stage (stage III/IV, BM, CNS) B-cell lymphoma. Under this system, LTLS is considered to be present if levels of two or more serum values of uric acid, potassium, phosphate, or calcium are more than or less than normal at presentation or if they change by 25% within 3 days before or 7 days after the initiation of treatment (Table 1). CTLS requires the presence of LTLS in addition to one or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias/sudden death, and seizures (Table 2). LTLS is considered to be either present or absent (Table 1), whereas the grade of CTLS is defined by the maximal grade of the clinical manifestation (Table 2).

Incidence and Risk Factors

TLS occurs most frequently in patients with NHL and other hematologic malignancies, particularly Burkitt's lymphoma, ALL, and

Table 1. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change From Baseline
Uric acid	≥ 476 μmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or ≥ 1.45 mmol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

NOTE. Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy.

acute myeloid leukemia (AML). In one case review study of 102 patients with high-grade NHL, LTLS was found in 42% of patients, although clinically significant symptoms, including life-threatening emergencies or requirements for specific therapy resulting from tumor lysis, occurred in only 6%.[4] In another study of 1,791 pediatric patients with NHL enrolled onto two multicenter trials, 78 children (4.4%) developed TLS.[6] Within the subgroup of patients who had either Burkitt's lymphoma or Burkitt's ALL (B-ALL), the rate of TLS development was 8.4%, whereas in the B-ALL–specific subgroup, a rate of 26.4% was observed, suggesting that patients with B-ALL were at the highest risk for developing the syndrome. In a third study, the rate of metabolic abnormalities consistent with TLS was 27% in 30 patients (median age, 11 years; range, 2 to 30 years) with Burkitt's lymphoma (six cases of hyperkalemia, two cases of hypocalcemia, two cases of hyperphosphatemia, and one case of lactic acidosis), with four resultant deaths, two of which were attributable to hyperkalemia.[7]

A fourth retrospective study was designed to examine the incidence of hyperuricemia and TLS, as well as associated health care costs, in 788 patients (433 adults, 322 children) with acute leukemia or NHL from Belgium, the Netherlands, Spain, and the United Kingdom.[8] Hyperuricemia was defined as blood level of uric acid greater than 6.5 mg/dL (371 μmol/L) in children and greater than 7 to 7.5 mg/dL (400 to 450 μmol/L) in adults. The overall incidence of hyperuricemia and TLS (LTLS or CTLS) was 18.9% and 5.0%, respectively. The rates were 14.7% and 3.4% in patients with AML, 21.4% and 5.2% in those with ALL, and 19.6% and 6.1% in patients with NHL, respectively. Finally, the rate of hyperuricemia was 18.9% in both the adult and pediatric populations, whereas rates of TLS were 4.8% and 5.3%, respectively.

A single-center retrospective chart review was conducted by Montesinos et al[9] to assess the incidence of TLS in 614 consecutive patients undergoing initial induction chemotherapy for AML. Prophylactic measures included intravenous (IV) hydration and allopurinol. Clinical or laboratory TLS developed in 101 patients (17%; 12% LTLS and 5% CTLS). Although there was no correlation between LTLS and death rate (21% v 24%; P = .51), CTLS was associated with an increased death rate (83% v 24%; P < .001), and in 14 patients, this was considered a major cause of death.

The syndrome is observed less frequently in other hematologic malignancies, including chronic lymphocytic leukemia (CLL),[10-12] indolent NHL,[13] and promyelocytic leukemia.[14] In a retrospective analysis of 6,137 patients with CLL who received treatment with fludarabine, TLS was suspected in 26 patients (0.42%), with clinical or laboratory features reported in 20 patients (0.33%).[15] TLS has also been reported in patients with NHL treated with the anti-CD20 monoclonal antibody rituximab.[16] In a postapproval analysis of 36,000 patients treated between November 1997 and May 1999, TLS

	Grade					
Complication	0	1	2	3	4	5
Creatinine*†	≤ 1.5 × ULN	1.5 × ULN	> 1.5-3.0 × ULN	> 3.0-6.0 × ULN	> 6.0 × ULN	Death
Cardiac arrhythmia*	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	—	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death

Table 2. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

NOTE. Laboratory tumor lysis syndrome and at least one clinical complication.
Abbreviations: ULN, upper limit of normal; CHF, congestive heart failure; ADL, activities of daily living.
*Not directly or probably attributable to therapeutic agent.
†If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 μmol/L; ≥ 12 to < 16 years, both male and female, 88 μmol/L; ≥ 16 years, female 105.6 μmol/L, male 114.4 μmol/L.

was estimated to have occurred in 0.04% to 0.05% of patients. Elevated numbers of circulating tumor cells (≥ 25,000 cells/μL) or a large tumor burden seemed to be associated with an increased risk of developing TLS.[16,17] Although occurrences are rare, a literature review revealed 45 case reports of TLS in patients with solid tumors, with a mortality rate of one in three in this patient set.[18] Finally, the enrollment demographics of two large international compassionate-use trials evaluating the utility of rasburicase in the initial management of individuals at high risk for the development of TLS suggest that there is a perceived risk in pediatric and adult patients with leukemias and lymphomas, including ALL, AML, chronic myeloid leukemia, CLL, and NHL[19,20] (Table 3).

Certain intrinsic tumor-related factors have been associated with an increased risk for the development of TLS, including high tumor cell proliferation rate, large tumor burden, tumor chemosensitivity, and increased lactate dehydrogenase (LDH) levels.[6,10,18,21] In addition, several conditions may predispose patients to developing TLS, such as preexisting uremia or hyperuricemia, decreased urinary flow or acidic urine, dehydration, oliguria, anuria, and renal insufficiency or renal failure.[7,8,16,22,23]

On the basis of this information, patients were stratified into low-, intermediate-, and high-risk groups. Stratification is based on type of malignancy, WBC counts, and type of therapy and is listed in Tables 4 and 5. Low-risk patients are defined as those with indolent NHL or other slowly proliferating malignancies. Patients with diffuse large-cell lymphoma or other rapidly proliferating malignancies are considered to be of intermediate risk for development of TLS. High-risk patients are defined as those having Burkitt's lymphoma, lymphoblastic lymphoma, and B-ALL. Patients with ALL, AML, and CLL are stratified by WBC levels.

Prevention and Management

The potential severity of complications resulting from the development of TLS necessitates measures for prevention in high-risk patients and prompts treatment in the event that symptoms arise. Recognition of risk factors, close monitoring of at-risk patients, and appropriate interventions are the key to preventing or managing TLS.

Table 3. Malignancies Commonly Diagnosed in Patients Perceived to Be at High Risk for Developing Tumor Lysis Syndrome[20]

Malignancy	Pediatric (n = 682)		Adult (n = 387)		Total (n = 1,069)	
	No.	%	No.	%	No.	%
Acute lymphoblastic leukemia	433	63	73	19	506	47
Acute myeloid leukemia	74	11	104	27	178	17
Chronic lymphocytic leukemia	0	0	37	10	37	3.5
Chronic myeloid leukemia	6	0.9	36	9	42	4
non-Hodgkin's lymphoma	122	18	109	28	231	22
Hodgkin's disease	8	1.2	6	1.6	14	1.3
Multiple myeloma	0	0	15	3.9	15	1.4
Other hematologic malignancies	5	0.7	3	0.7	8	0.7
Solid tumors	34	5	4	1	38	3.6

NOTE. Data represent consecutive patients enrolled onto a compassionate-use trial evaluating the efficacy and safety of rasburicase in patients with cancer who presented with, or were at risk of developing, hyperuricemia.

Table 4. Risk Factors for Tumor Lysis Syndrome

Characteristic	Risk Factor
Tumor type	Burkitt's lymphoma Lymphoblastic lymphoma Diffuse large-cell lymphoma ALL Solid tumors with high proliferative rates and rapid response to therapy
Tumor burden/extent of disease	Bulky disease (>10 cm) Elevated LDH (> 2× ULN) Elevated WBC (>25,000/μL)
Renal function	Preexisting renal failure Oliguria
Baseline uric acid	Baseline serum/plasma uric acid > 450 μmol/L (7.5 mg/dL)
Effective and rapid cytoreductive therapy	Disease-specific therapy, varies according to tumor type

Abbreviations: ALL, acute lymphoblastic leukemia; LDH, lactate dehydrogenase.

Fluids and hydration. Aggressive hydration and diuresis are fundamental to the prevention and management of TLS. The combination of hydration and enhanced urine flow promotes the excretion of uric acid and phosphate by improving intravascular volume, renal blood flow, and glomerular filtration.[24-26] The use of diuretics may also be necessary to maintain adequate urine output, but use of diuretics is contraindicated in patients with hypovolemia or obstructive uropathy.

Alkalinization. The use of sodium bicarbonate to alkalinize the urine had historically been recommended as part of TLS prevention and management strategies (eg, when using allopurinol).[27] However, it is not recommended with the use of recombinant urate oxidase (rasburicase). The solubility of uric acid at pH 5.0 is approximately 15 mg/dL, whereas it increases to approximately 200 mg/dL at pH 7.0, providing the rationale for alkalinization.[6] However, although alkaline urine promotes the excretion of uric acid, it does not substantially increase the solubility of xanthine and hypoxanthine.[24,25,28] Moreover, xanthine has low solubility (5 mg/dL at pH 5.0 and 13 mg/dL at pH 7.0).[5] In situations where levels of these metabolites are increased, such as after allopurinol treatment, this can lead to the precipitation of xanthine crystals in renal tubules, potentially resulting in xanthine-obstructive uropathies. In a study in rats, Conger et al[29] found that increasing urine flow rate was the most effective strategy for preventing urate-induced obstructive uropathy. In the absence of increased urine output, increasing urinary pH greater than 7.0 was ineffective in preventing uric acid crystallization. Thus, given the potential compli-

cations associated with alkalinization, such as metabolic alkalosis and calcium phosphate precipitation, and the lack of clear evidence demonstrating benefit, the use of sodium bicarbonate for the prevention and treatment of TLS is currently not recommended.

Allopurinol. One approach to preventing or managing TLS-associated hyperuricemia is to block the conversion of xanthine and hypoxanthine to uric acid (Fig 1). Allopurinol is a xanthine analog which, when converted in vivo to oxypurinol, acts as a competitive inhibitor of xanthine oxidase, thereby blocking the conversion of the purine metabolites to uric acid.[30,31] Use of allopurinol has been shown to decrease the formation of uric acid and to reduce the incidence of obstructive uropathy caused by uric acid precipitation in patients at risk for developing TLS.[30]

Since its introduction in 1965, oral allopurinol has demonstrated efficacy in inhibiting the formation of uric acid and reducing the incidence of uric acid–obstructive uropathy in patients at risk for TLS.[22,30,31] In a retrospective analysis of 1,172 patients treated with IV allopurinol, a level of activity comparable to the oral formulation was demonstrated.[32] When used as a treatment for patients with elevated uric acid levels, IV allopurinol reduced uric acid levels in 57% of adult patients (mean time to response, 5 days) and stabilized levels in an additional 30% (mean time to response, 2 days). In pediatric patients, uric acid levels improved in 88% of patients and stabilized in 7% (mean time to response, 1 day in both cases). When used prophylactically in patients at risk of developing TLS, it prevented an increase in

Table 5. Patient Stratification by Risk

| Type of Cancer | Risk | | |
	High	Intermediate	Low
NHL	Burkitt's, lymphoblastic, B-ALL	DLBCL	Indolent NHL
ALL	WBC ≥ 100,000	WBC 50,000-100,000	WBC ≤ 50,000
AML	WBC ≥ 50,000, monoblastic	WBC 10,000-50,000	WBC ≤ 10,000
CLL		WBC 10,000-100,000 Tx w/fludarabine	WBC ≤ 10,000
Other hematologic malignancies (including CML and multiple myeloma) and solid tumors		Rapid proliferation with expected rapid response to therapy	Remainder of patients

Abbreviations: NHL, non-Hodgkin's lymphoma; B-ALL, Burkitt's acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia, CLL, chronic lymphocytic leukemia; Tx, treatment; CML, chronic myeloid leukemia.

serum uric acid levels in 93% of adults and 92% of children. Mild to moderate skin or allergic reactions were reported in 10 cases.

However, although allopurinol has demonstrated efficacy in preventing and treating hyperuricemia and related complications in patients at risk for TLS, there are several limitations to its use. First, because allopurinol acts by decreasing the formation of uric acid, it is ineffective in reducing levels of uric acid developed before treatment. Because it may take several days for reductions in uric acid levels to occur,[32] delays in cytotoxic therapy, which could potentially exacerbate preexisting hyperuricemia, may be necessary. Second, allopurinol inhibits xanthine oxidase, thus blocking the catabolism of xanthine and hypoxanthine, resulting in an increase in the levels of these metabolites.[22,31] This can lead to a build-up and precipitation of xanthine crystals in the renal tubules, potentially leading to acute obstructive uropathy.[23,33,34] Third, allopurinol also reduces the clearance of other purine-based chemotherapeutic agents that are frequently used in the treatment of leukemia, such as 6-mercaptopurine and azothioprine, requiring dose reductions of these agents when used concomitantly with allopurinol.[35,36] Compared with urate oxidase treatment, allopurinol has been associated with reduced clearance of high-dose methotrexate owing to reduced renal function in these patients,[37] and it is contraindicated in combination with cyclophosphamide and other cytotoxic agents due to increased bone marrow suppression.[38] Finally, allopurinol has been associated with hypersensitivity reactions, which may be manifested as cutaneous rash or fever.

Nonrecombinant urate oxidase (uricozyme). A second approach to the management of hyperuricemia is to promote the catabolism of uric acid. In most mammals, there exists an enzyme, urate oxidase, that converts uric acid into allantoin, which is five to 10 times more soluble in urine than uric acid, H_2O_2, and CO_2.[39,40] However, this enzyme is not present in humans because of a nonsense mutation in the coding region. A nonrecombinant form of urate oxidase with a high specific activity was initially isolated from *Aspergillus flavus*.[41,42] Kissel et al[43] reported results of a phase I/II study in 61 adults demonstrating that nonrecombinant urate oxidase at a dose of 800 U/d reduced uric acid levels in the blood and increased allantoin excretion. A second study by Masera et al[44] demonstrated the efficacy of nonrecombinant urate oxidase in 30 pediatric patients with leukemia. Toxicities included allergic reactions and methemoglobinemia or hemolytic anemia in patients with a deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme.[45]

In a study of 134 pediatric patients treated with nonrecombinant urate oxidase from 1994 to 1996, Pui et al[46] reported that when compared with historical control patients treated with hyperhydration and allopurinol, nonrecombinant urate oxidase led to more rapid decreases in uric acid levels. Nearly 50% of patients in the nonrecombinant urate oxidase treatment cohort had urate concentrations less than 1 mg/dL after 2 days of therapy versus 2% of those treated with allopurinol ($P < .001$). In addition, median concentrations of urate in the blood were significantly lower in patients who received urate oxidase (0.6 mg/dL v 2.3 mg/dL; $P < .0001$), as were levels of creatinine (0.5 mg/dL v 0.7 mg/dL; $P = .01$) and urea nitrogen (11 mg/dL v 24 mg/dL; $P < .001$). However, 4.5% of patients developed hypersensitivity reactions after the first dose, likely as a result of impurities in the urate oxidase preparation, and one patient developed methemoglobinemia. More recently, Patte et al[47] reported that the use of nonrecombinant urate oxidase resulted in an 8.5% rate of TLS-associated

metabolic abnormalities in 57 patients with advanced Burkitt's lymphoma and B-cell ALL, with only 1.7% of patients requiring dialysis.

Recombinant urate oxidase (rasburicase). The gene encoding urate oxidase has now been cloned from *Aspergillus flavus* and expressed in a modified strain of *Saccharomyces cerevisiae*, allowing production and purification of the recombinant enzyme (rasburicase), potentially reducing the risk of contaminant-related allergic reactions.[48] The half-life for the elimination of rasburicase is approximately 16 hours and 21 hours with 0.15 mg/kg and 0.2 mg/kg dosing, respectively, with no apparent accumulation when the area under the curve was evaluated.

Pui et al[49] reported results from a phase I/II study evaluating the safety and efficacy of rasburicase in 131 patients ≤ 20 years of age (median age, 7 years) at risk for the development of hyperuricemia. Patients included in the study presented with B-lineage ALL (n = 62), T-cell ALL (n = 33), advanced-stage NHL (n = 30), B-cell ALL (n = 5), and AML (n = 1). Rasburicase was administered for 5 to 7 days, and chemotherapy could be started 4 hours after initiation of treatment. Results from the initial dose validation phase identified the effective dose as 0.2 mg/kg, which could be administered every 12 hours for the first 48 hours of the study. In the 65 patients who presented with hyperuricemia, median plasma uric acid levels decreased from 9.7 mg/dL at study entry to 1.0 mg/dL after treatment. In the remaining 66 patients, median plasma uric acid levels decreased from 4.3 mg/dL to 0.5 mg/dL ($P = .0001$). Daily median uric acid concentrations remained at 0.5 mg/dL throughout the treatment period. Serum phosphorus levels decreased to normal levels within 48 hours and decreased significantly in hyperuricemic patients within 4 days ($P = .0003$). Significant decreases in serum creatinine levels occurred after 24 hours, both in patients with and without hyperuricemia ($P = .0003$ and $P = .02$, respectively). Importantly, none of the patients required dialysis or developed other serious symptoms of TLS, and no severe adverse events were noted, although rasburicase-specific antibodies developed in 17 patients.

In an open-label multicenter randomized trial, Goldman et al[50] compared treatment with rasburicase to oral allopurinol in 52 pediatric patients with lymphoma (39 patients) or leukemia (13 patients) who were at high risk of developing TLS. All patients received approximately 3 L/m² of hydration daily. Average uric acid levels at study initiation were 7.1 mg/dL in the rasburicase group and 7.8 mg/dL in the allopurinol group. The mean area under the curve (uric acid plasma concentration v time) was significantly lower for patients treated with rasburicase (128 mg/dL/h $\pm$ 70 mg/dL/h) compared with those receiving allopurinol (329 mg/dL/h $\pm$ 129 mg/dL/h; $P < .0001$), for a 2.6-fold decrease in uric acid exposure in the rasburicase versus allopurinol treatment groups. Further, plasma uric acid levels were reduced by 86% in rasburicase-treated patients within 4 hours of the first dose, compared with 12% in allopurinol-treated patients ($P < .0001$). Mean creatinine levels decreased from 1.44 times the normal mean to 1.02 times the normal mean within 4 days in the rasburicase treatment group, whereas the concentration increased from 1.32 times the normal mean to 1.47 times the normal mean during the same period in patients treated with allopurinol. Severe hemolysis occurred in one patient treated with rasburicase, and no evidence of G6PD deficiency was detected.

The Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma study evaluated the efficacy and safety of prophylactic rasburicase therapy in 100 adult patients with

aggressive NHL during the first course of chemotherapy.[51] Patients received rasburicase at 0.20 mg/kg/d for 3 to 7 days, beginning 1 day before, or on the day of, chemotherapy initiation. Eleven percent of patients were considered hyperuricemic on study entry (uric acid > 450 mmol/L or > 7.56 mg/dL). Uric acid levels decreased within 4 hours of initial administration of rasburicase, and normalized uric acid levels were maintained throughout chemotherapy in all patients who received at least 3 days of treatment. In addition, no increase in creatinine levels was observed, and no patients required dialysis. Other metabolites, including phosphorus, calcium, and potassium, were also controlled during treatment. Rasburicase treatment was well tolerated, although three patients discontinued treatment early because of a grade 3 increase in liver enzymes.

PHARMACOECONOMICS OF RENAL FAILURE, HEMODIALYSIS, AND TUMOR LYSIS SYNDROME

In addition to the impact on morbidity and mortality, the economic consequences of renal failure with or without dialysis must also be considered. An analysis of the 1999 Health Care Utilization Project National Inpatient Sample, representing approximately 7 million hospital discharges in 20% of US community hospitals, including almost 600,000 patients with hematologic malignancies, was carried out by Candrilli et al.[52] Patients who developed acute renal failure requiring dialysis had an average hospital length of stay of 21 days and an average total cost per discharge of $51,990. In comparison, patients who did not develop acute renal failure had a mean length of stay of 7 days and an average cost of $9,978. A European analysis of 788 patients led by Annemans et al[8] also revealed much higher costs incurred by patients having TLS. In this study, the average cost of additional medical treatment for patients with hyperuricemia but not TLS was €672, whereas the costs for care of patients with hyperuricemia and TLS were approximately 11 times higher (€7,342; $P < .0001$).

Therefore, it has been proposed that prevention of renal failure and/or hyperuricemia and TLS would result in a net savings in health care costs. A pan-European analysis, also led by Annemans et al,[53] showed the cost-effectiveness of prevention of hyperuricemia/TLS with rasburicase. In this study, the incremental cost of prevention was divided by the average number of life-years saved to produce the incremental cost-effectiveness ratio (ICER) or the estimated cost per life-year saved, a measure of the economic value of rasburicase treatment. In pediatric patients with higher life expectancies, the ICER per life-year saved ranged from €425 to €3,054 depending on country; in adult patients with NHL or ALL, the ICERs of prevention ranged between €23,794 and €41,383 per life-year saved. Rasburicase treatment was less effective in adult patients with AML, with an ICER close to €100,000, perhaps owing to the limited life expectancy of these patients. These results suggest rasburicase usage in the initial management of high-risk patients is particularly cost-effective.

GUIDELINES

After reviewing the clinical data and standard practices regarding the management of TLS and its prevention in at-risk patients, the Expert Panel formulated the following guidelines. The Panel assigned levels of evidence and guideline grades based on systematic evaluation and weighting of clinical data (Table 6).

Table 6. Levels of Evidence and Grade of Recommendation

Level or Grade	Type of Evidence/Grade of Recommendation
Level	
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and false-negative errors (high power).
II	Evidence obtained from at least one well-designed, experimental study. Randomized trials with high false-positive or false-negative errors (low power).
III	Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, and time or matched case-control series.
IV	Evidence from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies.
V	Evidence from case reports and clinical examples.
Grade	
A	There is evidence of type I or consistent findings from multiple studies of type II, III, or IV.
B	There is evidence of type II, III, or IV and findings are generally consistent.
C	There is evidence of type II, III, or IV but findings are inconsistent.
D	There is little or no systematic empirical evidence.

Guidelines for Managing High-, Intermediate-, and Low-Risk Patients

In the case of pediatric patients, although those at high risk are clear candidates for aggressive intervention and those at low risk might be observed only, the classification and treatment approach for intermediate-risk patients is still not clearly defined (Fig 2). The best management of TLS is prevention. Adequate hydration and urine output are of high importance in preventing TLS.

Along with hydration, rasburicase should be used in the initial management of pediatric patients considered to be at high risk. Additionally, these patients should be admitted to an intensive care unit or similarly monitored nursing area of the hospital. If the nurse-to-patient ratio is favorable, the patient may be placed on a standard hospital floor with close monitoring, but the patient should have ready access to intensive care unit facilities if his or her clinical condition deteriorates. A renal expert should be notified regarding the patient in case dialysis is required. Delaying tumor therapy until these measures can be taken will help prevent TLS and its complications, but the aggressive nature of many malignancies will require a case-by-case decision based on the patient's condition (level of evidence: II; grade of recommendation: A).

For intermediate-risk pediatric patients, in addition to hydration, allopurinol may be used as an initial antihyperuricemic treatment as described in Allopurinol Administration. Initial management with a single dose of rasburicase might also be considered in pediatric patients[54,55] (level of evidence: V; grade of recommendation: D).

For pediatric patients unlikely to develop TLS, it is the opinion of the panel that a watch-and-wait approach with close monitoring is entirely appropriate (level of evidence: V; grade of recommendation: D).

The above recommendations are valid for adult patients, although the US Food and Drug Administration has not approved rasburicase for use in adult or geriatric patients in the United States.
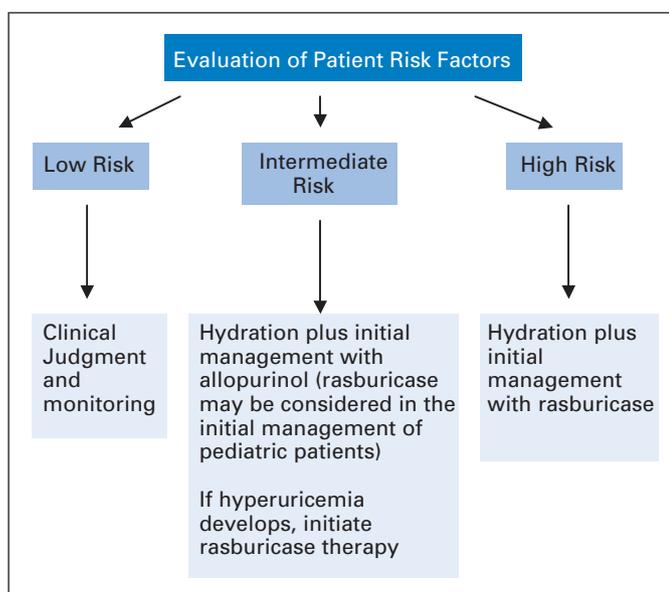
Fig 2. Treatment algorithm for prevention and management of hyperuricemia. The treatment approach for low-risk patients is observation. The best treatment approach for those with intermediate risk is still under development, but rasburicase is recommended if hyperuricemia develops despite prophylactic treatment with allopurinol. Aggressive intervention is necessary for high-risk patients. Vigorous hydration is recommended for all patients in the middle-to-high risk groups and those with diagnosed tumor lysis syndrome (TLS). The use of rasburicase is recommended for the treatment of patients with hyperuricemia associated with diagnosed TLS or in the initial management of pediatric patients considered to be at high risk of developing TLS.

The expert panel noted that in Europe, rasburicase has been used in the initial management of high- and intermediate-risk adult patients (level of evidence: V; grade of recommendation: B).

Management of Hyperuricemia

Hydration. As mentioned previously, the mainstay of prophylaxis for and treatment of TLS remains adequate hydration.[24-26] Vigorous hydration is recommended for all patients in the intermediate-to-high risk groups or for those with diagnosed LTLS or CTLS, with the exception of patients presenting with renal failure or oliguria. It is important to attempt to achieve equal fluid intake and urinary output if at all possible.

Pediatric patients should receive 2 to 3 L/m^2/d (or 200 mL/kg/d if ≤ 10 kg; volume adapted to patient age, cardiac function, and urine output) IV of a solution consisting of one quarter of normal saline/5% dextrose. Urine output should be monitored closely and be maintained within a range of 80 to 100 mL/m^2/h (4 to 6 mL/kg/h if ≤ 10 kg).[5] If there is no evidence of acute obstructive uropathy and/or hypovolemia, diuretics may be used to maintain output within this range if necessary. Because of the concurrent risks of hyperkalemia, hyperphosphatemia, and/or calcium phosphate precipitation, potassium, calcium, and phosphate should be withheld initially from hydration fluids. Urine-specific gravity should be monitored and maintained at ≤ 1.010[5] (level of evidence: V; grade of recommendation: D).

Guidelines for hydration in adult patients are the same as those for pediatric patients. Fluid intake should be maintained at approximately one to two times maintenance, with a urine output of 80 to 100 mL/m^2/h (level of evidence: V; grade of recommendation: D).

Alkalinization. Historically, alkalinization had been recommended for pediatric patients receiving treatment for hyperuricemia, particularly those treated with allopurinol, to promote excretion of uric acid in the urine. However, this practice is currently not recommended, because there is no unequivocal evidence of efficacy. Further, alkalinization may increase the risk of precipitation of calcium phosphate crystals. Because of these potential complications and lack of evidence of benefit, it is the consensus of the panel that alkalinization is only indicated for patients with metabolic acidosis, in which case sodium bicarbonate may be considered based on the standards of the institution. No consensus was reached among panel members regarding alkalinization for patients who will receive treatment with allopurinol. Considerations such as high urine pH and phosphate levels may preclude the use of sodium bicarbonate in these patients. Alkalinization is additionally not required in patients receiving rasburicase (level of evidence: V; grade of recommendation: D).

Allopurinol Administration

The use of allopurinol can be considered as a prophylactic option for patients with a medium risk of developing TLS (Table 7). Allopurinol is contraindicated in patients with a pre-existing allergy to allopurinol or who develop a severe hypersensitivity reaction while receiving treatment with this agent.

In pediatric patients, allopurinol is administered at a dose of 50 to 100 mg/m^2 every 8 hours orally (maximum dose, 300 mg/m^2/d) or 10 mg/kg/d divided every 8 hours (maximum dose, 800 mg/d). For patients unable to take allopurinol orally, IV administration may be considered, at a dose of 200 to 400 mg/m^2/d in one to three divided doses (maximum dose, 600 mg/d).[32,56]

Treatment with allopurinol should be initiated in intermediate-risk patients no more than 12 to 24 hours before the start of induction chemotherapy. Treatment may be continued until uric acid levels are normalized, and tumor burden, WBC count, and other laboratory

Table 7. Administration of Antihyperuricemic Agents[5]	
Agent	Recommendation
Allopurinol	Dosing: 100 mg/m^2/dose every 8 hours (10 mg/kg/d divided every 8 hours) PO (maximum, 800 mg/d) or 200-400 mg/m^2/d in 1-3 divided doses; IV (maximum, 600 mg/d) Reduce dose by 50% or more in renal failure Reduce 6-mercaptopurine and/or azathioprine doses by 65%–75% with concomitant allopurinol May need to adjust doses of dicumarol, thiazide diuretics, chlorpropamide, cyclosporine, or allopurinol when they are used concomitantly with allopurinol
Rasburicase	Contraindicated in glucose-6-phosphate dehydrogenase–deficient patients, as well as in patients with a known history of anaphylaxis or hypersensitivity reactions, hemolytic reactions, or methemoglobinemia reactions to rasburicase or any of the excipients Administration: intravenously over 30 minutes according to dosages recommended in Table 8 Uric acid levels should be monitored regularly and used as a guide to modulate dosing; to measure uric acid levels place blood sample immediately on ice to avoid continual pharmacologic ex vivo enzymatic degradation 10% incidence of antibody formation

Abbreviations: PO, orally; IV, intravenously.

values have returned to low-TLS risk levels as defined in Table 7. It should be noted that allopurinol only prevents the formation of uric acid and does not reduce uric acid produced before the initiation of treatment. Therefore, for patients with preexisting hyperuricemia (≥ 450 μmol/L or 7.5 mg/dL), treatment with rasburicase is preferred (level of evidence: II; grade of recommendation: B).

Allopurinol can also cause an increase in serum levels of the purine precursors xanthine and hypoxanthine.[22,31] Because of the lower solubility of xanthine in urine, there is the risk of xanthine crystal deposition in the renal tubules, which can result in acute obstructive uropathy.[23,33,34] In addition, because allopurinol also reduces the degradation of other purines, particularly 6-mercaptopurine, dose reductions of 50% to 70% of 6-mercaptopurine and/or azathioprine are recommended when this agent is administered concomitantly with allopurinol.[36]

Because allopurinol is excreted by the kidneys, a dose reduction of 50% is recommended in patients with renal insufficiency. Other drugs with potential to interact with allopurinol include dicumarol, uricosuric agents, thiazide diuretics, ampicillin/amoxicillin, cyclophosphamide and other cytotoxic agents, chlorpropamide, and cyclosporine.

The guidelines for allopurinol dosages and administration for adult patients are the same as those for pediatric patients. Treatment may be started 1 to 2 days before the start of induction chemotherapy and may be continued for up to 3 to 7 days afterwards, based on the ongoing risk of TLS development (level of evidence: II; grade of recommendation: B).

Recombinant Urate Oxidase Administration and Treatment Duration

The use of recombinant urate oxidase (rasburicase) is recommended for the treatment of pediatric patients with hyperuricemia associated with LTLS or CTLS, or in the initial management of patients considered to be at high risk of developing TLS (Table 5). In addition, for patients in the intermediate-risk group, rasburicase is recommended if hyperuricemia develops despite prophylactic treatment with allopurinol (level of evidence: II; grade of recommendation: B).

Rasburicase is contraindicated in patients with a known G6PD deficiency (certain patients of African American, Mediterranean, or Southeast Asian descent) and in pregnant or lactating females.[48] Screening for G6PD deficiency should include a thorough history of prior drug-induced hemolytic anemia, ethnic background, and available semiquantitative laboratory tests. Definitive testing, including measurement of RBC NADPH formation is recommended. There is limited experience of using rasburicase in patients with a history of asthma or significant atopic allergy.

The US Food and Drug Administration–approved dosing guidelines recommend 0.15 to 0.2 mg/kg once daily in 50 mL of normal saline as an IV infusion over 30 minutes for 5 days.[48] However, on the basis of data gathered during compassionate-use trials, rasburicase has demonstrated activity even at lower doses and for shorter duration. Therefore, expert practice suggests a dose of 0.10 to 0.2 mg/kg daily, dependent on whether the intention is prevention or treatment (Table 8). Duration of treatment can range from 1 to 7 days,[19,20,49-51,57] with an average of 3 days observed on the 1,069-patient compassionate-use trial.[20] It is important that uric acid levels be monitored regularly and used as a guide to modulate dosing with rasburicase. In certain cases, such as in patients experiencing massive tumor lysis, it may be necessary to increase the administration schedule to twice daily. The length of treatment is related to control of plasma uric acid levels, and therefore clinical judgment should be used. Treatment is not necessary when uric acid is extremely low or no longer detectable.

Potential serious adverse reactions are rare and include anaphylaxis, rash, hemolysis, methemoglobulinemia, fever, neutropenia (with or without fever), respiratory distress, sepsis, and mucositis. Other adverse reactions include vomiting, fever, nausea, headache, and diarrhea.[58]

At room temperature, rasburicase will cause the degradation of uric acid within blood samples, thereby interfering with accurate measurement. Therefore, samples should immediately be placed on ice until the completion of assay, which is preferably done within 4 hours of collection.

Guidelines for rasburicase usage in adults are identical to those provided above for pediatric patients. However, it should be noted that the US Food and Drug Administration has not approved rasburicase for use in adult or geriatric patients in the United States (level of evidence: II; grade of recommendation: B).

OTHER CONSIDERATIONS

A history of allergy was not listed as a contraindication for administration of rasburicase, although known history of hypersensitivity to urate oxidase is. There are few data on the use of rasburicase in these patients, as they were excluded from clinical trials. However, anecdotal evidence suggests that rasburicase may be used in patients with a history of allergy without severe adverse events, and a clinical study is ongoing in this patient subpopulation.

It is the opinion of the expert panel that after initial management with rasburicase, the subsequent use of allopurinol is not necessary. However, there are currently no data demonstrating whether patient outcome is better or worse with allopurinol after initial treatment with rasburicase. An ongoing clinical study will address this question.

Table 8. Recommended Rasburicase Dosing

| Tumor Lysis Syndrome Profile | Baseline Uric Acid | | Dose (mg/kg) | Duration* |
	mg/dL	mmol/L		
High risk	> 7.5	450	0.20	Based on plasma uric acid levels
Intermediate risk	< 7.5	450	0.15	Based on plasma uric acid levels
Low risk	< 7.5	450	0.10†	Clinical judgment

*The average duration of therapy is 2 days, but can vary from 1 day to 7 days.
†Dosages as low as 0.05 mg/kg have been used successfully in groups of patients in at least one clinical trial.[56]

Management of Hyperphosphatemia

It is of particular importance to treat hyperphosphatemia in pediatric patients (Table 9). For asymptomatic hyperphosphatemia, initial treatment consists of eliminating phosphate from intravenous solutions, maintaining adequate hydration, and the administration of phosphate binders. For severe hyperphosphatemia, hemodialysis, peritoneal dialysis, or continuous venovenous hemofiltration has been used (level of evidence: V; grade of recommendation: D).

Aluminum hydroxide 50 to 150 mg/kg/d is administered in divided doses orally or nasogastrically every 6 hours.[5] Its use should be limited to 1 to 2 days to avoid cumulative aluminum toxicity. Because pediatric patients might find the taste of aluminum hydroxide objectionable, other phosphate binders, such as calcium carbonate (eg, low calcium levels), sevelamer hydroxide, and lanthanum carbonate may alternatively be used.[59] Calcium carbonate should not be used in patients with elevated calcium levels. Phosphate clearance was found to be better with hemodialysis as compared with continuous venovenous hemofiltration or peritoneal dialysis.[22,60,61]

The above recommendations are valid for adult patients (level of evidence: V; grade of recommendation: D).

Management of Hyperkalemia

In pediatric patients, oral and IV sources of potassium should be eliminated as long as the risk of TLS exists (Table 9). Immediate intervention is indicated if serum potassium is greater than 7.0 to 7.5 mEq/L or the ECG shows widening of QRS complex. For asymptomatic patients, the standard treatment is sodium polystyrene sulfonate 1 g/kg with 50% sorbitol administered orally or rectally (avoid this route in neutropenic patients).[5] For symptomatic patients, more intense intervention is recommended, such as rapid-acting insulin (0.1 U/kg administered IV) and glucose infusion (25% dextrose 2 mL/kg).[5] Sodium bicarbonate (1 to 2 mEq/kg administered via IV push) can be

given to induce influx of potassium into cells. Calcium gluconate (100 to 200 mg/kg/dose) via slow infusion with ECG monitoring for bradycardia can be given for treatment of life-threatening arrhythmias. However, sodium bicarbonate and calcium should not be administered through the same line (level of evidence: V; grade of recommendation: D).

Elevated potassium levels should be verified immediately with a second sample to rule out fictitious hyperkalemia from hemolysis during phlebotomy. Patient ECG and cardiac rhythm should be closely followed, along with evaluation of electrolyte levels.

The above recommendations are valid for adult patients (level of evidence: V; grade of recommendation: D).

Management of Hypocalcemia

For asymptomatic pediatric patients, no intervention is recommended[5] (Table 9). Symptomatic patients may be treated with calcium gluconate 50 to 100 mg/kg IV, administered slowly with EKG monitoring[5] (Level of evidence: V; grade of recommendation: D).

Care must be taken because increased calcium might increase the risk of calcium phosphate precipitation in the tissues and consequential obstructive uropathy.[5] If the patient's phosphate levels are high, the panel noted that a renal consultation might be necessary.

The above recommendations are valid for adult patients (level of evidence: V; grade of recommendation: D).

MONITORING GUIDELINES (OPTIONS AND EVALUATION OF CLINICAL TESTS AND METHODS)

Pediatric patients at high risk for developing TLS should have laboratory and clinical TLS parameters monitored 4 to 6 hours after the initial administration of chemotherapy. The TLS parameter consists

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Table 9. Management of Electrolyte Abnormalities[5]	
Abnormality	Management Recommendation
Hyperphosphatemia	
Moderate, ≥ 2.1 mmol/L	Avoid IV phosphate administration Administration of phosphate binder
Severe	Dialysis, CAVH, CVVH, CAVHD, or CVVHD
Hypocalcemia, ≤ 1.75 mmol/L	
Asymptomatic	No therapy
Symptomatic	Calcium gluconate 50-100 mg/kg IV administered slowly with ECG monitoring
Hyperkalemia	
Moderate and asymptomatic, ≥ 6.0 mmol/L	Avoid IV and oral potassium ECG and cardiac rhythm monitoring Sodium polystyrene sulphonate
Severe (> 7.0 mmol/L) and/or symptomatic	Same as above, plus: Calcium gluconate 100-200 mg/kg by slow IV infusion for life-threatening arrhythmias Regular insulin (0.1 U/kg IV) + D25 (2 mL/kg) IV Sodium bicarbonate (1-2 mEq/kg IV push) can be given to induce influx of potassium into cells. However, sodium bicarbonate and calcium should not be administered through the same line. Dialysis
Renal dysfunction (uremia)	Fluid and electrolyte management Uric acid and phosphate management Adjust renally excreted drug doses Dialysis (hemo- or peritoneal) Hemofiltration (CAVH, CVVH, CAVHD, or CVVHD)

Abbreviations: IV, intravenous; CAVH, continuous arterial-venous hemodialysis; CVVH, continuous veno-venous hemofiltration; CAVHD, continuous arterial-venous hemodialysis; CVVHD, continuous veno-venous hemodialysis.

of levels of uric acid, phosphate, potassium, creatinine, calcium, and LDH, as well as fluid input and urine output. For all patients, uric acid levels should be re-evaluated 4 hours after administration of rasburicase and every 6 to 8 hours thereafter until resolution of TLS, for example, until normalization of LDH levels (level of evidence: V; grade of recommendation: D).

If possible, patients with a high risk of developing TLS (ie, patients with Burkitt's lymphoma) should be in a position to be readily transferred to an intensive care unit before beginning chemotherapy.

For adult intermediate-risk patients, the panel suggested that patients be monitored for at least 24 hours after the completion of chemotherapy. For multiagent chemotherapeutic regimens in which the different drugs are administered over several days, monitoring should continue for 24 hours after the administration of the final agent of the first cycle. If rasburicase is not used in the initial management of the patient, electrolyte levels should be determined 8 hours after chemotherapy, which might require a 1-night hospital stay. The panel noted that if TLS has not occurred after 2 days, the likelihood is essentially zero that the patient will experience TLS (level of evidence: V; grade of recommendation: D).

GUIDELINES FOR THE USE OF DIALYSIS

For pediatric and adult patients at high risk of TLS, cytotoxic chemotherapy should only be administered once patients are located in a facility with ready access to dialysis. Although dialysis usage has been reduced since the introduction of rasburicase, as many as 3% of patients (1.5% of pediatric patients and 5% of adult patients) still require this procedure.[20] A nephrology specialist should therefore be notified in advance regarding high-risk patients. The panel recommended that a renal consultation be obtained immediately if urine output is low, if there is persistent or elevated phosphate levels, or in the case of hypocalcemia.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

CORRECTIONS

The June 1, 2008, review article by Coiffier et al, entitled "Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome: An Evidence-Based Review" (J Clin Oncol 26:2767-2778, 2008), contained an error.

In the Background section, under Prevention and Management, the second to last sentence of the sixth paragraph stated that allopurinol is contraindicated in combination with capecitabine, whereas it should have noted a contraindication in combination with cyclophosphamide and other cytotoxic agents, as follows:

"Compared with urate oxidase treatment, allopurinol has been associated with reduced clearance of high-dose methotrexate owing to reduced renal function in these patients,[37] and it is contraindicated in combination with cyclophosphamide and other cytotoxic agents due to increased bone marrow suppression."[38]

The online version has been corrected in departure from the print. The authors apologize to the readers for the mistake.

The April 20, 2009, article by Cesaro et al, entitled "Prospective, Randomized Trial of Two Different Modalities of Flushing Central Venous Catheters in Pediatric Patients With Cancer" (J Clin Oncol 27:2059-2065, 2009), contained an error.

In the first sentence of the Introduction section, the term "Port-a-Cath (Bard)" was used, whereas it should have been "totally implantable catheters," as follows:

"Tunnelled central venous catheters (CVCs), such as Broviac-Hickman (Bard, Rome, Italy) and totally implantable catheters, provide safe and reliable vascular access for delivery of chemotherapy and supportive therapies."[1,2]

PORT-A-CATH is a registered trademark of Smiths Medical (St Paul, MN). The authors apologize to the readers for the mistake.

The December 10, 2009, article by Wick et al, entitled "NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide" (J Clin Oncol 27:5874-5880, 2009), contained errors.

In Table 1, *IDH-1* wild-type was given as 62 for radiotherapy and 66 for PCV or temozolomide, whereas it should have been 36 and 31, respectively. In addition, *IDH-1* mutated was given as 36 for radiotherapy and 31 for PCV or temozolomide, whereas it should have been 62 and 66, respectively.

The authors apologize to the readers for the errors.

The November 10, 2009, article by Bilimoria et al, entitled "National Assessment of Melanoma Care Using Formally Developed Quality Indicators" (J Clin Oncol 27:5445-5451, 2009), contained an error. The article was not written on behalf of the Melanoma Quality Indicator Development Expert panel as indicated in the sidebar.

Journal of Clinical Oncology apologizes to the authors and readers for the mistake.

The January 1, 2010, article by Denkert et al, entitled "Tumor-Associated Lymphocytes As an Independent Predictor of Response to Neoadjuvant Chemotherapy in Breast Cancer" (J Clin Oncol 28:105-113, 2010), contained errors.

In Figure 2, the data in parts F through I were labeled as CD3, whereas they should have been labeled as CD20 in parts F and G and as CXCR3 in parts H and I.

The online version has been corrected in departure from the print. *Journal of Clinical Oncology* apologizes to the authors and readers for the mistakes.